REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-2, 16, 31-32, 34-42 and 44-56 are pending. Claims 8-9, 15, 17, 22-23, 29-30 and 39-42 were withdrawn from consideration by the Examiner. Applicants have canceled claims 3-15, 17-30, 33 and 43 without prejudice to future prosecution of that subject matter.

Restriction Requirement

Reconsideration of the final restriction requirement is requested.

Each of the proteins having the amino acid sequences of SEQ ID NOS:3-6 is not "a polyketide synthase" as alleged in the Office Action but "a subunit of polyketide synthase." As shown in Figures 1 and 2, avermectin aglycon synthase is encoded by both AveAI (SEQ ID NO:1) and AveAII (SEQ ID NO: 2) and comprises four ORFs, which encode polypeptides having amino acid sequences of SEQ ID NOS:3-6, respectively. As such, four subunit polypeptides (SEQ ID NOS:3-6) have related and similar functions which constitute together avermectin aglycon synthase. Therefore, all of those amino acid sequences should be examined in the same application linked by original claim 1 (drawn to the avermectin aglycon synthase gene).

It is also noted that claim 34 was indicated as withdrawn on page 2 of the Office Action, but it was then rejected under Section 112, 102 and 103 in the same Office Action. Claim 34 is drawn to a vector comprising the DNA coding for the polypeptide of SEQ ID NO:3 and should be included in Group I. Therefore, Applicants submit that withdrawal of claim 34 was a mistake because it has been examined on the merits.

Specification/Claim Objections

Formal drawings with the correction required by the Examiner are submitted herewith. Entry and approval of the corrected formal drawings are requested.

Claims 1-7, 10-14, 16, 18, 20-21, 26-28, 31-33, 35-36, 38 and 43 were objected to under 37 CFR § 1.75(d)(1) as allegedly being in improper form because those claims

recite improper Markush groups. Members of Markush groups in the pending claims members share a common utility and substantial structural feature.

Claims 16 and 35-37 were objected to under 37 CFR § 1.75(c) as allegedly being in improper form because those claims cannot depend on another multiple dependent claim. Proper multiple dependent claims are pending.

Claims 5-7, 10-14, 20-21, 24-27 and 33 were objected to as allegedly informal. Those claims have been canceled without prejudice or disclaimer.

Withdrawal of the objections is requested.

35 U.S.C. - Utility

Claims 1-7, 10-14, 16, 18-21, 24-28, 31-33 and 43 were rejected under Section 101 because they are allegedly "directed to non-statutory matter." Applicants traverse because independent claims 1-2, 31-32 and 44 are directed to "isolated" DNA or polypeptide. Claims 16 and 47 do not need to recite "isolated" because they are not naturally occurring forms of DNA or polypeptide, but are artificially modified forms thereof.

Withdrawal of the Section 101 rejection is requested.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

The specification was objected to and claim 37 was rejected under Section 112, first paragraph, because it was alleged that "the specification lacks a sufficient written description for enablement based on [a] deposit requirement." Applicants traverse.

Enclosed is a copy of the receipt for a deposit of *Streptomyces avermitilis* K2038 with the Fermentation Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (now the National Institute of Advanced Industrial Science and Technology, an independent administrative institution under the Ministry of Economy, Trade and Industry, which is located at Tsukuba Central 6,

Higashi 1-1-1, Tsukuba, Ibaraki, Japan) on February 26, 1990 under accession No. FERM BP-2775. It was deposited under the Budapest Treaty, and will be irrevocably and without restriction or condition released to the public upon the issuance of the patent. The specification and claim 37 satisfy the written description requirement.

Claims 1, 3-4, 31, 34-36 and 38 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse.

Claims 1 and 31 refer to a nucleotide sequence represented by Nos. 1-11916 of SEQ ID NO:1, an amino acid sequence represented by SEQ ID NO:3, or derivatives thereof (e.g., the artificially modified forms). Claims 3-4 have been canceled without prejudice or disclaimer.

Claim 31 depends from claim 44 and is directed to a polypeptide encoded by a DNA that hybridizes with the DNA consisting of a nucleotide sequence represented by nucleotide Nos. 1-11916 of SEQ ID NO:1 under stringent conditions and encodes a polypeptide having AT' activity, ACP' activity, KS1 activity, AT1 activity, KR1 activity, ACP1 activity, K52 activity, AT2 activity, DH2 activity, KR2 activity, and ACP2 activity. The phrase "stringent conditions" is supported by the description in the specification on page 4, lines 13-21, and does not constitute new matter.

Claims 34-36 are drawn to a recombinant vector or a transformant comprising the DNA of claims 1, 2, 16, and 44-46; claim 38 is drawn to a process for producing the polypeptide of claims 31-32 and 47-48 using the transformant.

Therefore, Applicants submit that the specification provides an adequate written description of the claims.

Finally, in contradiction to the assertions made in the Office Action, the four sub-unit polypeptides (SEQ ID NOS:3-6) have related and similar functions.

Withdrawal of the written description rejections made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1, 3-4, 16, 31-33, 35-36, 38 and 43 were rejected under Section 112, first paragraph, because it was alleged that "[t]he specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims." Applicants traverse.

Claims 1, 16 and 32 refer to a nucleotide sequence represented by Nos. 1-11916 of SEQ ID NO:1, an amino acid sequence represented by SEQ ID NO:3, or derivatives thereof (e.g., the artificially modified forms). Claims 3-4, 33 and 43 have been canceled without prejudice or disclaimer.

Claim 16 is drawn to DNA encoding a polypeptide comprising an amino acid sequence wherein His, residue at position 3037 is substituted by an amino acid other than His, and Ala residue at position 3038 is substituted by an amino acid other than Ala in the amino acid sequence represented by SEQ ID NO:3.

Claim 31 depends from claim 44 and is directed to a polypeptide encoded by a DNA that hybridizes with the DNA consisting of a nucleotide sequence represented by nucleotide Nos. 1-11916 of SEQ ID NO:1 under stringent conditions and encodes a polypeptide having AT' activity, ACP' activity, KS1 activity, AT1 activity, KR1 activity, ACP1 activity, K52 activity, AT2 activity, DH2 activity, KR2 activity, and ACP2 activity. A

person skilled in the art is able to obtain a DNA that hybridizes with the nucleotide sequence represented by nucleotide Nos. 1-11916 of SEQ ID NO:1 and has the same activity as that of the polypeptide of SEQ ID NO:3 in accordance with the techniques taught in this specification (page 4, line 22, to page 5, line 8). Enzyme activity is assayed, for example, according to Example 2 of this specification. In particular, assays can be performed by transforming *Streptomyces avermitilis* K2038 by homologous recombination between the obtained DNA and the endogenous gene encoding the polypeptide of SEQ ID NO:3, and then detecting the production of avermectin aglycon synthase.

Claims 35-36 are drawn to a transformant comprising the DNA of claims 1, 2, 16, and 44-46; claim 38 is drawn to a process for producing the polypeptide of claims 31-32 and 47-48 using the transformant. Claim 45 is drawn to the DNA of claim 16 wherein the amino acid other than His is Tyr, and the amino acid other than Ala is Glu. Claim 46 is drawn to the DNA of claim 45 wherein the DNA comprising a nucleotide sequence 5'-CATGCC-3' of nucleotide Nos. 9109-9114 of SEQ ID NO:1 is replaced by a nucleotide sequence 5'-TACGAG-3'.

A person skilled in the art is able to obtain the modified DNA encoding a polypeptide comprising an amino acid sequence in which one or more amino acids are substituted in accordance with the description of the specification (page 13, lines 6-16, and Example 2). In particular, Example 2 shows a method for producing DNA encoding a polypeptide comprising an amino acid sequence wherein His residue at position 3037 is substituted by Tyr, and Ala residue at position 3038 is substituted by Glu. The recombinant vector, the transformant, and the production of avermectin aglycon synthase or modified avermectin aglycon synthase by the transformant is easily achieved by a person skilled in the art in accordance with the description of the specification (page 30, line 17, to page 44, line 16).

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1-7, 10-14, 16, 18-21, 24-28, 31-33, 35-38 and 43 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The term "avermectin aglycon synthase" is not recited in claims 1-2, 16, 31-32 and 35-38 because that limitation is not required for patentability. Claims 3-7, 10-14, 18-21, 24-28, 33 and 43 have been canceled without prejudice or disclaimer.

In claim 44, "stringent conditions" are specifically defined based on page 4 of the specification as described above and the "activity" of a polypeptide encoded by the DNA is also defined as AT' activity, ACP' activity, KS1 activity, AT1 activity, KR1 activity, ACP1 activity, K52 activity, AT2 activity, DH2 activity, KR2 activity, and ACP2 activity.

The phrase "a polypeptide comprising an amino acid sequence wherein one or more amino acids are deleted, replaced, or added in the amino acid sequence of SEQ ID NO:3" is not recited in the pending claims because that limitation is not required for patentability.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 3-4, 34-36 and 43 were rejected under Section 102(b) as allegedly anticipated by Gewain et al. (U.S. Patent 5,262,474). Applicants traverse.

Gewain et al. (the '474 patent) describe cloning of the 110-kb gene cluster from *Streptomyces avermilitis*. But they do not teach or suggest any nucleotide sequence of DNA coding for the polypeptide represented by an amino acid sequence of SEQ ID NO:3 as required by claim 1 (see also the polypeptide of claim 32). Claims 31 and 44 require a DNA which hybridizes to a nucleotide sequence represented by Nos. 1-11916 of SEQ ID NO:1 under stringent conditions. Claims 34-36 are also based on these sequences, which are neither taught nor suggested by Gewain et al. Therefore, the claimed invention is not anticipated by the '474 patent.

Claims 1, 3-4, 31, 34-35 and 43 were rejected under Section 102(b) as allegedly anticipated by Marsden et al. (Science 279:199-202, 1998). Applicants traverse.

Marsden et al. describe the construction of a two-hybrid polyketide synthase consisting of AT' and ACP' domains. It does not, however, teach or suggest the cloning of DNA coding for a polypeptide having the amino acid sequence of SEQ ID NO:3 comprising AT', ACP', KS1, AT1, KR1, ACP1, K52, AT2, DH2, KR2, and ACP2 domains or the nucleotide sequence of that DNA.

The activity of the two hybrid polyketide synthase consisting of AT' and ACP' domains as disclosed by Marsden et al. and the activity of the polypeptide encoded by DNA comprising a nucleotide sequence represented by Nos. 1-11916 of SEQ ID NO:1 are completely different due to differences in structure. In particular, the two-hybrid polyketide synthase does not have the activity of AT', ACP', KS1, AT1, KR1, ACP1, KS2, AT2, DH2, KR2, and ACP2 domains. In contrast, the polypeptide encoded by the DNA of claim 2 or 44 has all these activities. Also, the DNA coding for the two-hybrid polyketide synthase and the DNA of claims 2 or 44 have completely different nucleotide sequences. Therefore, the claimed invention is not anticipated by Marsden et al.

Withdrawal of the Section 102 rejections is requested because all limitations of the claimed invention are not disclosed by the cited references.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Claims 2-7, 10-14, 18-21, 24-28 and 34-37 were rejected under Section 102(b) as allegedly anticipated by or, in the alternative, under Section 103 as allegedly obvious over Gewain et al. (U.S. Patent 5,262,474). Applicants traverse.

Gewain et al. (the '474 patent) describe cloning of the 110-kb gene cluster from *Streptomyces avermilitis*. But the '474 patent does not teach or suggest any nucleotide sequence of DNA coding for the polypeptide represented by an amino acid sequence of SEQ ID NO:3. Therefore, the claimed invention is not anticipated or rendered unpatentable in view of the '474 patent.

It was alleged in the Office Action that a person of ordinary skill in the art would have been able to sequence the gene cluster and to identify the various open reading frames that include the polypeptide having the starter domain and modules 1 and 2. This is incorrect because the '474 patent neither teaches nor suggests the locations of the starter domain and modules 1 and 2 on the cloned gene cluster.

MacNeil (Biotechnology 28:421-442, 1995) discloses that various modules and catalytic domains are assumed to be present in the avermectin aglycon synthase; most of the nucleotide sequence of the modules and domains, however, are still unknown (see Fig. 15-9 of MacNeil in which 15 question marks "?" are shown).

Applicants determined the complete nucleotide sequence of an avermectin aglycon synthase gene (full length), and thereby found that the gene had a length of over 60 kb and consisted of 12 modules comprising various domains. The order of domains in each module was found to be common between modules 1, 4, 5, and 7, and was also common between modules 2, 6, 10 to 12. The homology between module 1 and module 4, 5, or 7 was 56.0% to 72.4% and those between module 2 and module 6, 10, 11, or 12 was 64.5% to 86.2%. As such, it would have been difficult for a person of ordinary skill in the art to identify a module of avermectin aglycon synthase from a partial nucleotide sequence.

It is difficult to determine the module or domain described in MacNeil in which the 110 kb gene cluster described in '474 patent is involved. Thus, the DNA coding for the polypeptide of SEQ ID NO:3 cannot be obtained based on the disclosure of the '474 patent and Marsden et al. It was only obtained by Applicants through the complete sequencing of the avermectin aglycon synthase gene (full length).

In fact, the GC content of Streptomyces DNA is generally very high and that of *Streptomyces avermitilis* is 70.7% (see the abstract of Nat. Biotechnol. 21:526-531, 2003, which is enclosed). It is difficult to determine the complete sequence of DNA with high GC content at the time of filing of the application since it is likely to cause compression and to form secondary structures. In order to overcome the above problems, many attempts such as a DNA polymerase reaction under conditions where secondary structure of DNA is formed with difficulty were applied. No previous attempt was successful, however, because of low efficiency or excessively complicated and time consuming reactions (see Molecular Cloning, page 13.74 1989, which is enclosed). Consequently, complete sequencing of the DNA with a length of over 60 kb required much time and excessive effort.

Thus, it would have been difficult to determine the complete sequence of the avermectin aglycon synthase gene based on the disclosures of the '474 patent and MacNeil. It would also have been also difficult to obtain the vector, the host cell, or the recombinant avermectin aglycon synthase using the DNA encoding the polypeptide having the amino acid sequence of SEQ ID NO:3. Moreover, it would have been difficult to obtain the modified polyketide synthase based on the disclosure of Marsden et al. This shows that a person of ordinary skill in the art would not have had a reasonable expectation of success.

Claims 2-5, 10-11, 18-19, 24-25, 31 and 34-35 were rejected under Section 102(b) as allegedly anticipated by or, in the alternative, under Section 103 as allegedly obvious over Marsden et al. (Science 279:199-202, 1998). Applicants traverse.

Marsden et al. describe the construction of a two-hybrid polyketide synthase consisting of AT' and ACP' domains. It does not, however, teach or suggest the cloning of DNA coding for a polypeptide having the amino acid sequence of SEQ ID NO:3 comprising AT', ACP', KS1, AT1, KR1, ACP1, K52, AT2, DH2, KR2, and ACP2 domains or the nucleotide sequence of that DNA. Therefore, the claimed invention is not anticipated or rendered unpatentable by Marsden et al.

Claims 16, 31-33 and 38 were rejected under Section 103 as allegedly unpatentable over Gewain et al. (U.S. Patent 5,262,474) in view of MacNeil (Biotechnology 28:421-442, 1995) and Marsden et al. (Science 279:199-202, 1998). Applicants traverse.

As explained above, a person of ordinary skill in the art would not have had a reasonable expectation of success to obtain DNA encoding a polypeptide having AT' activity, ACP' activity, KSI activity, AT1 activity, KR1 activity, ACP1 activity, K52 activity, AT2 activity, DH2 activity, KR2 activity, and ACP2 activity based on the disclosures of Gewain et al. and Marsden et al. Therefore, the claimed invention is patentable. Moreover, the mutations(s) recited in claims 16 and 45-48 are neither taught nor suggested by the cited references.

Withdrawal of the Section 103 rejections is requested because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 13), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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